JOC Article

Single-Isomer Trisubstituted Olefins from a Novel Reaction of (*E*)-*β*-Chloro-α-iodo-α,*β*-unsaturated Esters and Amides

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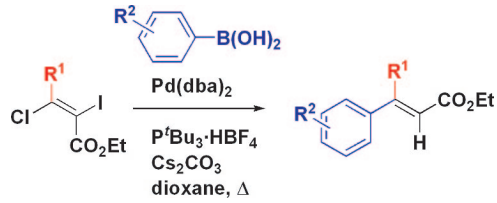

(*E*)-*β*-Chloro-α-iodo-α,*β*-unsaturated esters are converted to single isomer trisubstituted olefins bearing three different carbon substituents by cross-coupling under reflux. Mechanistic investigations suggest that this process transfers a hydrogen from the boronic acid to the α-position of the substrate and then introduces an aryl group to the *β*-position of the intermediate template while replacing chloride. The reaction is highly stereoselective, showing preference for the *E*-isomer. The process proceeds through (*E*)-*β*-chloro-α-aryl-α,*β*-unsaturated esters that are transformed efficiently into the corresponding *E*-products through stereoselective Suzuki-type reactions giving single isomers. The observed stereochemistry is apparently enabled by the intermediacy of a palladium allenoate. The reaction involves a catalytic cycle in which Pd^{II} is reduced to Pd^{0} through the formation of biaryl-coupled products.

Introduction

The task of synthesizing trisubstituted olefins bearing three different carbon-linked appendages is a significant challenge in organic synthesis. Phosphorus-based reactions such as the Wittig and Horner−Wadsworth−Emmons, while powerful, provide mixtures of *E* and *Z* isomers.[1] More successful are indirect methods such as the carbometalation of alkynes involving either alkyl or hydride transfer,[2] the conversion of existing olefin templates using cross couplings,[3] or Heck-type reactions.[4] Selectivity issues may arise during these processes producing isomeric mixtures that may be extremely difficult to resolve. Thus, there exists a need for simple, direct methods to prepare trisubstituted olefins that provide reliable means of generating single isomer products.

Results and Discussion

We recently developed a mild and versatile method of synthesizing acyclic, single isomer olefins bearing four different carbon-linked substituents.[5] These alkenes were obtained using an (*E*)-*β*-chloro-α-iodo-α,*β*-unsaturated ester template that was submitted to sequential Sonogashira coupling reactions to produce trans ene−diynes. In order to improve the scope of this process, the development of a Suzuki coupling process[6] was initiated with the goal of introducing a wider variety of

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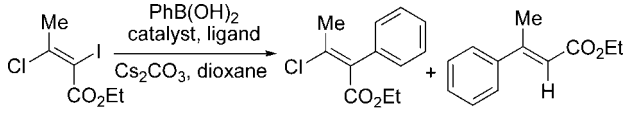
TABLE 1. Attempted Generation of (*Z*)-β-Chloro-α,β-unsaturated Ester 2 from (*E*)-β-Chloro-α-iodo-α,β-unsaturated Ester 1

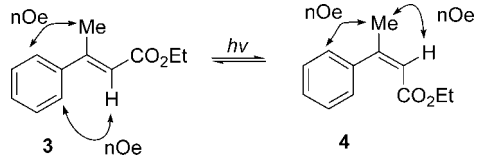


1 2 3

entry[a]	catalyst	ligand	product[b]
1	$Pd(PPh_3)_4$		NR
2	$PdCl_2(PPh_3)_2$		NR
3	$PdCl_2$(dppf)		NR
4	$Pd_2(dba)_3$	P(*t*-Bu)$_3$·HBF_4	NR
5[c]	$Pd_2(dba)_3$	P(*t*-Bu)$_3$·HBF_4	**3** (99%)

[a] Conditions: 0.1 equiv of catalyst, 0.2 equiv of ligand, 4.0 equiv of $PhB(OH)_2$, 3.0 equiv of Cs_2CO_3, dioxane, rt. [b] Isolated yield in parentheses. [c] Reaction performed at reflux.

SCHEME 1. Elucidation of the Structure of Trisubstituted Olefin 3

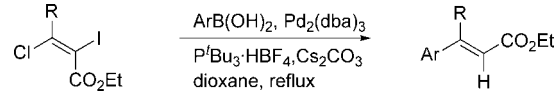


substituents to the α-position of the substrate.[7] An initial experiment performed using $Pd(PPh_3)_4$ in dioxane gave no conversion to the desired product **2** (Table 1, entry 1). Similar results were obtained using $PdCl_2(PPh_3)_2$ and with the bidentate ligand DPPF (entries 2 and 3), while the use of P(*t*-Bu)$_3$ as a ligand also was unsuccessful (entry 4). In order to increase reactivity, we carried out a coupling reaction using $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ in refluxing dioxane. As shown in entry 5, a clean conversion of all of the starting material was realized.

The product of the reaction was isolated as a single isomer, and spectroscopic analysis immediately indicated that it was not the anticipated product **2**. Instead, a trisubstituted olefin was obtained in which a phenyl group and hydrogen had been introduced onto the olefin moiety. Using NOESY analysis, we established that the product of the reaction was the trisubstituted olefin **3**. This process also produced a quantitative amount of biphenyl, a result that became important when considering the mechanism of the process (see below).

As shown in Scheme 1, the key reaction product **3** gave NOE interactions between the methyl and phenyl groups and between the phenyl and olefinic hydrogen. Photoisomerization of compound **3** gave olefin **4** that displayed enhancements between the phenyl and methyl hydrogens and between the methyl and olefinic hydrogen. This network of NOE effects indicated that the phenyl and olefinic hydrogen were cis in adduct **3**. The regiochemistry of compound **3** was established from the magnitude of the coupling constant between this hydrogen and the methyl group (1.3 Hz) and by the observation that the olefinic hydrogen gave only one NOE interaction for both isomers (**3** and **4**). The phenyl residue of product **3** displayed two NOE effects, one with the methyl group and one with the olefinic hydrogen, and the methyl group of **4** experienced the two NOE enhancements shown. This network would only be possible if the phenyl was β to the ester group in both compounds and if the stereochemistry of the initial product **3** was *E* as shown.[8]

TABLE 2. Formation of Trisubstituted Olefins from (*E*)-β-Chloro-α-iodo-α,β-unsaturated Compounds and Boronic Acids



entry[a]	R	substrate	Ar	product	yield[b] (%)
1	Me[c]	**1**	C_6H_5	**3**	99
2	Me	**1**	4-$MeOC_6H_4$	**5**	83
3	Me	**1**	3-$MeOC_6H_4$	**6**	79
4	Me	**1**	2-$MeOC_6H_4$	**7**	98
5	Me	**1**	4-MeC_6H_4	**8**	76
6[d]	Me	**1**	4-FC_6H_4	**9**	69
7	Me	**1**	C_6H_5CHCH	**10**	88
8	Me	**1**	2-thiophene	**11**	82
9	Me	**1**	1-naphthyl	**12**	96
10	Me	**1**	2-naphthyl	**13**	54[9]
11	Cy	**14**	C_6H_5	**15**	71
12	$TBSO(CH_2)_2$	**16**	C_6H_5	**17**	81
13	$BnO(CH_2)_2$	**18**	C_6H_5	**19**	96
14	$TIPSO(CH_2)_2$	**20**	C_6H_5	**21**	95[10]
15[e]	$Me(CH_2)_5$	**22**	C_6H_5	**23**	99
16[e]	$Me(CH_2)_5$	**22**	4-$MeOC_6H_4$	**24**	92

[a] Conditions: 0.1 equiv of $Pd_2(dba)_3$, 0.2 equiv of P(*t*-Bu)$_3$·HBF_4, 10.0 equiv of $ArB(OH)_2$, 7.5 equiv of Cs_2CO_3, dioxane, reflux, 4 h. [b] Isolated yield. [c] 4.0 equiv of $ArB(OH)_2$ and 3.0 equiv of Cs_2CO_3 were used. [d] P(*t*-Bu)Me_2·HBF_4 was used in place of P(*t*-Bu)$_3$·HBF_4. [e] Weinreb amide was used; $Pd(OAc)_2$ was used in place of $Pd_2(dba)_3$.

In order to establish the scope of this unusual reaction, the effect of changing the boronic acid and of changing the substituent at the β-position of the template was explored (Table 2.) In addition to the simple phenyl moiety, aryl groups containing a variety of substituents could be introduced to the (*E*)-β-chloro-α-iodo template **1** to give the corresponding trisubstituted olefins. The presence of electron-donating groups on the aryl boronic acid was well tolerated, and excellent yields of the trisubstituted products were realized, even if the substituent was in the meta or ortho position (entries 2−5). The presence of a fluorine at the para position of the phenylboronic acid resulted in a lower recovery of the trisubstituted product, and a modest improvement in yield was realized by using P(*t*-Bu)Me_2 as the ligand in this case. Vinyl boronic acids underwent the process affording a very good recovery of the trisubstituted olefin product bearing a styrenyl appendage (entry 7). Heterocycles such as thiophene were compatible with the reaction, and we were pleased to note that hindered substituents such as 1- and 2-naphthyl groups could be successfully introduced (entries 8−10).

Substitution on the substrate template was tolerated as branched alkyl groups could be present in addition to functionalized alkyl moieties (entries 11−14). The reaction conditions

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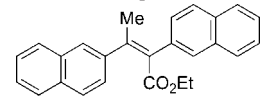
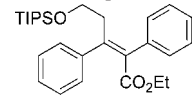
(8) Similar analyses were carried out for all products described in this work.

(9) 14% of a tetrasubstituted olefin product was obtained.



(10) 5% of a tetrasubstituted olefin product was produced.



SCHEME 2. Possible Elimination/Addition Mechanism To Account for the Formation of Products of Type 27 from 1

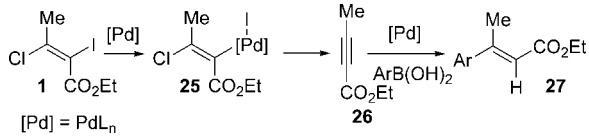
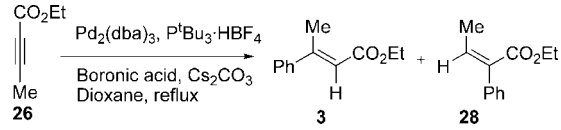


TABLE 3. Alkynyl Esters Submitted to the Conditions Used To Prepare Trisubstituted Esters



entry[a]	boronic acid	ratio(**3**:**28**)	combined yield (%)
1	$PhB(OH)_2$	3:1	10
2	$PhB(OD)_2$	2:1	10[b]
3[c]	$PhB(OH)_2$	3:1	50
4[d]	$PhB(OH)_2$	2:1	30

[a] Conditions: 0.1 equiv of $Pd_2(dba)_3$, 0.2 equiv of $P(t\text{-}Bu)_3 \cdot HBF_4$, 4.0 equiv of $ArB(OH)_2$, 3.0 equiv of Cs_2CO_3, dioxane, reflux, 4 h. [b] 46% Deuterium incorporation. [c] 7.1 equiv of water was added. [d] 0.1 equiv of **1** was added.

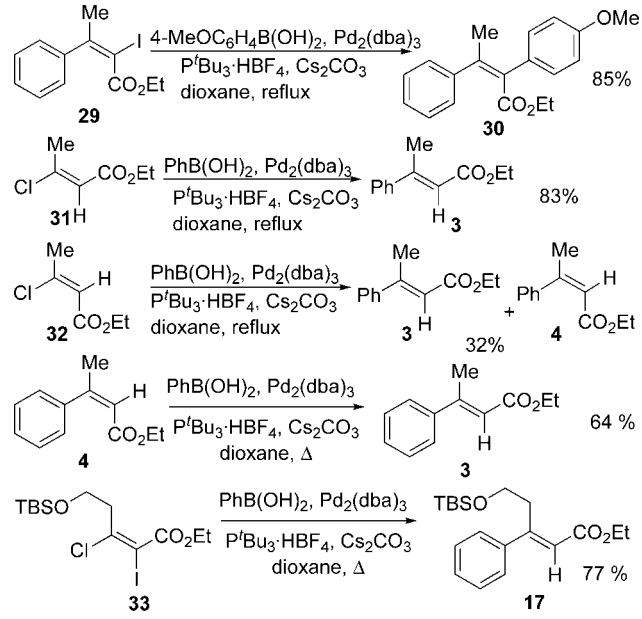
were compatible with the presence of other electron-withdrawing groups on the substrates as the use of a Weinreb amide in place of an ester group (compound **22**) gave excellent conversions to products (entries 15 and 16). In all of the examples shown in Table 2, the products were isolated as single isomers suggesting a highly specific or stereocontrolled reaction.

The observation of single isomers, in which the configuration of the olefin was "inverted" with respect to the starting substrate, was intriguing, and the mechanism by which this transformation had occurred was not immediately evident. The source of hydrogen was also unclear. This could have been introduced by simple protonation, or as part of a catalytic cycle involving palladium that would imply hydride transfer from a reductive elimination. To resolve these issues, a mechanistic analysis was carried out.

The fact that the aryl group and hydrogen were introduced in a cis fashion suggested a mechanism involving an intermediate alkyne. This process could have happened through an initial oxidative addition of Pd into the C−I bond of **1** followed by the elimination of chloride[11] to afford an alkynyl ester such as **26** (Scheme 2.) Such materials have been reported as side products during Negishi couplings of α,β-dibromo-α,β-unsaturated esters.[3h] The alkynyl ester would then suffer Pd-catalyzed aryl addition, followed by hydrogen transfer to form the products observed.[12]

To test whether such an elimination/addition mechanism was operative in the present process, alkynyl ester **26** was subjected to the reaction conditions. As shown in Table 3, when alkynyl ester **26** was treated with $PhB(OH)_2$ in the presence of palladium catalyst, a very low conversion to products was observed (entry 1). More importantly, the reaction produced a 3:1 mixture of trisubstituted olefin **3** and the *regioisomer* **28**,[13] a product that was not formed when **1** was used as a substrate. Performing the reaction with $PhB(OD)_2$ gave the analogous deuterated

SCHEME 3. Possible Reaction Intermediates Subjected to the Conditions Used To Form Trisubstituted Olefins



products, but the level of D incorporation in the products was only 46% (entry 2), suggesting that traces of water were implicated in the process. When a small amount of water was introduced to the medium, the yield was increased, but the same two regioisomers (**3** and **28**) were formed in similar ratios to the reaction performed without water (entries 1 and 3). To explore the possibility that substrate **1** was perhaps forming some sort of catalytic entity that was responsible for the selectivity noted (relative to the reaction without **1**), 10 mol % of **1** was added to the reaction mixture. In this experiment, the combined yield of products **3** and **28** was slightly increased (relative to the reaction performed without **1**); however, no significant change in product distribution was noticed (entry 4). Overall, these results suggested that the formation of trisubstituted olefins from (*E*)-β-chloro-α-iodo-α,β-unsaturated esters did *not* involve the intermediacy of an alkynyl ester such as **26**.

Eliminating alkynes such as **26** as reaction intermediates indicated that the process must involve sequential replacement of the halogens during palladium-catalyzed couplings. Previous experience with (*E*)-β-chloro-α-iodo-α,β-unsaturated esters had shown that the iodide was always replaced first during related cross-coupling reactions.[5,7] Experiments were performed to elucidate the order of substitution in the current process by subjecting possible intermediates to the reaction conditions. If the chloride at the β-position of **1** had been replaced first, then iodide **29** should be converted to **3** (Scheme 3.) When (*E*)-α-iodo-α,β-unsaturated ester **29**[14] was treated with 4-$MeOC_6H_4$-$B(OH)_2$ under the reaction conditions, tetrasubstituted olefin **30** was obtained as the sole product in 85% yield. The formation of the tetrasubstituted product **30**, rather than the trisubstituted derivative **3**, suggested that **29** could not be a reaction intermediate and that the iodide was indeed displaced first when substrates such as **1** were coupled with boronic acids under the present conditions.

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(14) Prepared following a procedure similar to that described in: Klein, J.; Levene, R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1971.
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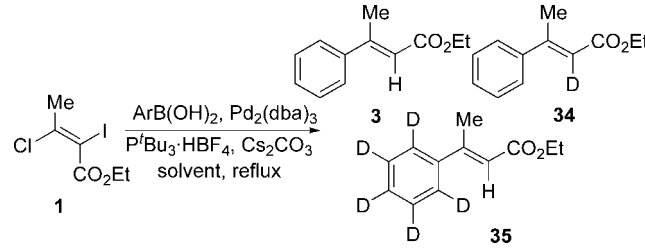
If the initial step of the reaction was the replacement of the iodide by hydrogen, the intermediate β-chloro-α,β-unsaturated esters thus formed (**31** or **32**) should be cleanly converted to product **3**. Subjecting the *cis*-chloride **31**[15] to the reaction conditions produced the expected trisubstituted olefin **3** in good yield as a single isomer. In the case of the *trans* β-chloro substrate **32**,[13] a low conversion to products was observed. Moreover, this reaction produced a 1.7:1 mixture of stereoisomers **3** and **4**. The fact that **31** was efficiently converted to product **3**, whereas the use of **32** led to an erosion in both selectivity and yield, indicated that the stereochemistry of the product was most likely established during the first step of the process and that intermediates such as **31** were implicated. A thermodynamic component to the process was suggested when the *Z* product isomer **4**[16] was subjected to the reaction conditions. The observation of only the *E* product **3** from this experiment suggested that **3** was thermodynamically favored at reflux in the presence of the reaction components. However, the selective formation of **3** from **1** could not simply be a consequence of thermodynamic control in the product, as suggested by the experiments involving the intermediate chlorides **31** and **32**.

That the stereochemistry of the product was indeed a consequence of the iodide replacement step was further suggested by performing a coupling reaction with the (*Z*)-β-chloro-α-iodo-α,β-unsaturated ester **33** that delivered the *E*-trisubstituted olefin **17** as the sole product in excellent yield. Interestingly, it was found that the reaction of the cis isomer **33**, with $PhB(OH)_2$ in the presence of $Pd_2(dba)_3$, $P(t\text{-}Bu)_3 \cdot HBF_4$, and Cs_2CO_3 in refluxing dioxane, was more facile than the conversion of the trans isomer **16** to products. The cis compound **33** could be converted to product **17** by a reaction performed at room temperature, whereas the trans material **16** required refluxing conditions to transform into the adduct **17** (Table 2, entry 12). If the intermediate chloride structure was indeed an *E* isomer similar to **31** (and not to the *Z* isomer **32**), then the reaction of the (*E*)-β-chloro-α-iodo-α,β-unsaturated ester **31**, possessing the same relative stereochemical arrangement of substituents, would perhaps be expected to proceed faster than that of the corresponding *Z* isomer. The results obtained with substrate **33** therefore also supported the intermediacy of **31** in the process.[17]

The possible sources of hydrogen were investigated using a series of isotopic-labeling experiments (Table 4.) Performing the reaction in deuterated acetonitrile resulted in no deuterium incorporation, indicating that the solvent was not the source of hydrogen. Although the yield of this process was lower than the standard reaction in dioxane, trisubstituted olefin **3** was obtained as the sole product of the reaction (as a single isomer) and the efficiency of the process was unaffected by the use of labeled solvent (entries 2 and 3). Previous reports involving rhodium-catalyzed additions of aryl boronic acids to alkynes had suggested that the phenyl ring of the boronic acid could serve as a supply of hydrogen atoms in some cases.[2a] When $C_6D_5B(OH)_2$ was used as a coupling partner, compound **35** was obtained as the sole product with no deuterium incorporation noted on the alkene moiety (entry 4). This indicated that the aryl ring was not

TABLE 4. Deuterium-Labeling Experiments To Elucidate the Source of Hydrogen Transfer



entry[a]	boronic acid	solvent	product	yield (%)
1	$PhB(OH)_2$	dioxane	**3**	99
2	$PhB(OH)_2$	CH_3CN	**3**	35
3	$PhB(OH)_2$	CD_3CN	**3**	32
4	$C_6D_5B(OH)_2$	dioxane	**35**	98
5	$PhB(OD)_2$	dioxane	**3**:**34** (48:52)[b]	89
6	$PhB(OH)_2$[c]	dioxane	**3**:**34** (33:67)	88
7	$PhB(OD)_2$[d]	dioxane	**3**:**34** (48:52)[b]	87
8	PhB_{pin}[e]	dioxane		NR
9	PhB_{pin}[e,c]	dioxane	**34**	40

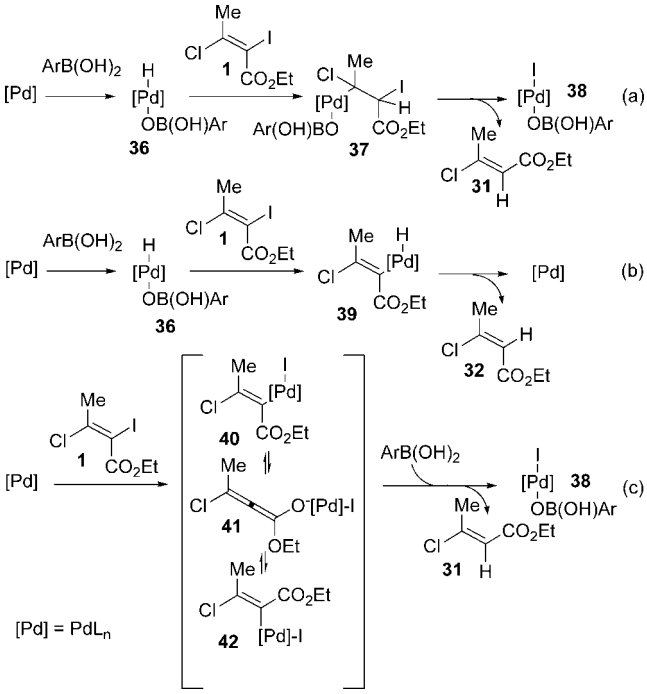
[a] Conditions: 0.1 equiv of $Pd_2(dba)_3$, 0.2 equiv of $P(t\text{-}Bu)_3 \cdot HBF_4$, 4.0 equiv of $ArB(OH)_2$, 3.0 equiv of Cs_2CO_3, dioxane, reflux, 2 h. [b] 52% deuterium-labeled boronic acid was used. [c] 7.1 equiv of D_2O added. [d] Reaction performed in the presence of 4 Å molecular sieves. [e] PhBpin = phenylboronic acid pinacol ester.

the source of hydrogen. The next possibility examined was the boronic acid (entry 5). Using $C_6H_5B(OD)_2$ as the coupling partner resulted in the formation of adduct **34** in which the level of deuterium incorporation (52%) matched that of the starting boronic acid (52%), suggesting that the hydrogen could be derived from the boronic acid component. When a reaction using $C_6H_5B(OH)_2$ was performed in the presence of 7 equiv of D_2O, deuterated product **34** was also formed. The ratio of **3** to **34** approximately matched the ratio of $PhB(OH)_2$ to D_2O in this experiment, suggesting that the hydrogen source could have been either the boronic acid, water, or the -ate complex formed from the water and boronic acid (entry 6). Although the reactions depicted in Table 2 were all performed under anhydrous conditions, it was possible that traces of water could be involved. An experiment using $PhB(OD)_2$ was therefore done in the presence of 4 Å molecular sieves, which produced a mixture of **3** and **34** in the same ratio as that observed previously (entries 5 and 7). When the pinacol ester of the boronic acid was used (entry 8), no product was formed consistent with the requirement for boronic acid as the hydrogen source. The same experiment, performed in the presence of 7 equiv of D_2O. resulted in the formation of product **34** indicating that hydrogen could be transferred from a boron−ate complex or from traces of water in the medium (entry 9).[6]

Several pathways were considered to account for the introduction of hydrogen onto the trisubstituted olefin product **3**. In principle, the hydrogen could be transferred formally as a hydride through reductive elimination from a palladium species (Scheme 4, pathways a and b) or by simple protonolysis (Scheme 4c). Two sequences were examined when considering the possibility of hydride transfer. Oxidative addition of Pd into the H−O bond of $ArB(OH)_2$ would generate species such as **36**.[10,18] This could be followed by a Heck-type addition pathway[19] delivering the hydride to

(16) A 10:1 mixture of **4** and **3** was used.
(17) The results obtained using **31**, **32**, and **33** as substrates are consistent with the intermediacy of a product in which the hydrogen and chloride were cis. This suggests that the thermodynamic preference for the *E* isomer **3** (scheme 3) may be coincidental.
(18) Shirakawa, E.; Otsuka, H.; Hayashi, T. *Chem. Commun.* **2005**, *47*, 5885.
(19) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156.

SCHEME 4. Possible Pathways Considered To Account for the Introduction of Hydrogen



form **37** as an intermediate (sequence a). A subsequent elimination of **38** from this material would form **31**, which would then undergo cross coupling to afford **3**. Although this mechanism could account for the stereochemistry of the products, electronically this process would be expected to favor regioisomers such as **28** rather than the observed products **3** as the hydride would be expected to add in a conjugate fashion to the α,β-unsaturated ester. In addition, if this mechanism were operative, (*Z*)-β-chloro-α-iodo-α,β-unsaturated esters would be expected to form products such as **4** selectively. As the reaction of **32** was inefficient and condensation of **33** gave the *E*-trisubstituted product **17** and not the *Z* isomer, an alternative process was indicated.

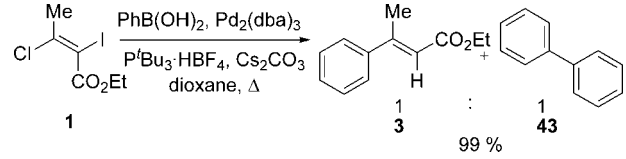
This second possibility would involve an exchange between the initial Pd hydride **36** and the substrate **1** to afford a precursor (**39**) for reductive elimination (sequence b). One difficulty with this sequence was that it predicted the formation of the *Z* products and of the intermediacy of **32** rather than **31** from the reductive elimination.[20] A more serious difficulty with this pathway was the fact that a transient palladium(IV) species would be implicated during the conversion of **36** to **39**, making this route an unlikely possibility.

A sequence considered was that initial oxidative addition of palladium(0) into the carbon−iodine bond of **1** would form an intermediate (**40**) that was formally a palladium enolate (sequence c). Introduction of the hydrogen could proceed by simple protonolysis,[21] a mechanism that would also provide a means of establishing the stereochemistry of the intermediates and products. At reflux, the palladium structure **40** could exist in equilibrium with the corresponding palladium allenoate **41** and therefore with isomeric palladium species **42**. Protonation of compound **42**, if more facile than the protonation of the initial intermediate **40**, could account for

(20) Related couplings using these substrates always proceed with retention of configuration. See refs[5] and.[7]

(21) Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123.

SCHEME 5. Isolation of a Biphenyl Byproduct during the Formation of Trisubstituted Olefin 3 from Substrate 1



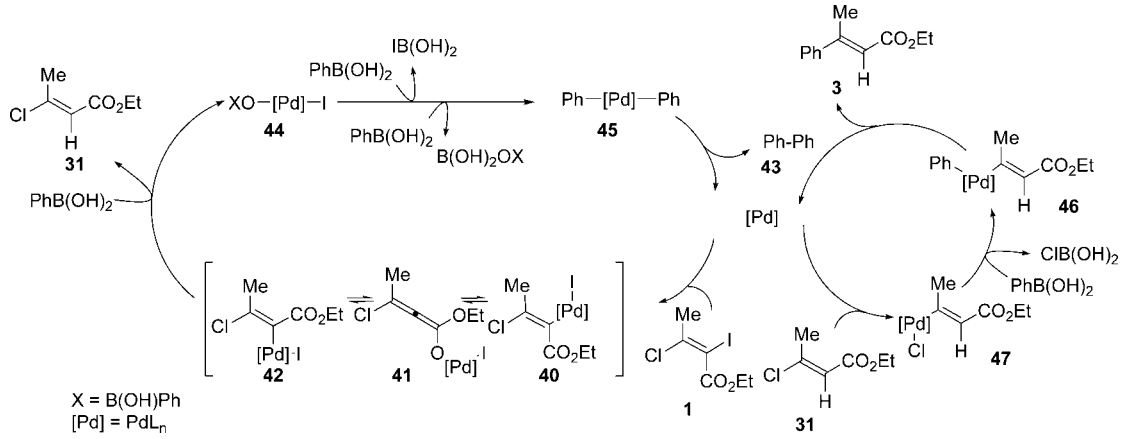
the stereochemistry of the products. This mechanism would be compatible with the results obtained with substrates **31** and **32**, which showed that the *cis*-chloride **31** was efficiently converted to **3**, whereas *trans*-chloride **32** showed erosions in both yield and stereochemistry during the final coupling phase. The difficulty with this mechanism was that such a protonolysis (**42** → **31**) would result in the production of a palladium(II) species (**38**) that would need some mechanism of conversion to the catalytically capable palladium(0) complex.

The formation of biphenyl compounds such as **43** as byproducts in the coupling reaction of **1**, in amounts equal to the amount of products formed, provided a means to account for this (Scheme 5.) Successive transmetalation steps involving excess boronic acid in the medium could ultimately form a diaryl palladium species that would suffer reductive elimination to regenerate the active Pd^0 catalyst while expelling biphenyl **43**. The observation of a stoichiometric amount of biphenyl byproduct **43** from the reaction of **1** with phenylboronic acid is consistent with this hypothesis.

On the basis of these results, a plausible mechanism involving two catalytic cycles is proposed that accounts for the formation of one single trisubstituted isomer from the Suzuki reaction of (*E*)-β-chloro-α-iodo-α,β-unsaturated esters such as **1** (Scheme 6.) The first step involves oxidative addition of the palladium into the carbon−iodine bond of **1** to form an (*E*)-alkenyl Pd^{II} species **40**. Under reflux conditions, this species would be in equilibrium with the palladium allenoate **41** and the isomeric (*Z*)-alkenylpalladium complex **42**. A protonolysis step involving the boronic acid would form the Pd^{II} intermediate **44**, while selectively generating chloride **31**. Successive transmetalation steps involving excess boronic acid in the medium could ultimately form the diaryl palladium species **45** that would suffer reductive elimination to regenerate the active Pd^0 catalyst while expelling biphenyl **43**. The observation of a stoichiometric amount of biphenyl product **43** from the reaction of **1** with phenylboronic acid is consistent with this hypothesis. The second catalytic cycle would follow the usual Suzuki−Miyaura mechanism using the (*E*)-β-chloro-α,β-unsaturated ester **31** as an entry point. The fact that **31** was efficiently converted to the final product **3** suggested that **31** was implicated in the cycle and not the isomeric chloride **32**.

A regiospecific and stereoselective palladium-catalyzed cross-coupling reaction of organoboronic acids onto β-chloro-α-iodo-α,β-unsaturated esters has been developed to produce single isomer trisubstituted olefins in excellent yields. This methodology is potentially a very useful synthetic tool as it gives single isomers and therefore avoids problematic olefin isomer separation. The mechanism of this process is somewhat unusual and involves protonolysis of an intermediate palladium allenoate in a highly stereoselective manner to afford intermediate (*E*)-β-chloro-α,β-unsaturated esters. This protonolysis is mediated by the boronic acid component in the mixture. The (*E*)-β-chloro-α,β-unsaturated

SCHEME 6. Proposed Catalytic Cycle



ester intermediates then rapidly undergo a stereoselective Suzuki-type coupling to deliver the final products as single isomers. The protonolysis and final coupling are "matched" in that the isomer produced in the initial proton transfer is the substrate most efficiently converted to products by the cross-coupling process.

Experimental Section

General Procedure for the Synthesis of Trisubstituted Alkenes from (*E*)-3-Chloro-2-iodo-2-alkenoates. (*E*)-Ethyl 2-Methyl-3-phenylbut-2-enoate (3). To an oven-dried, 10 mL, round-bottom flask equipped with a Teflon sleeve and a water-cooled condenser were added $Pd_2(dba)_3$ (16 mg, 0.018 mmol), P(*t*-Bu)$_3$·HBF$_4$ (21 mg, 0.072 mmol), $PhB(OH)_2$ (88 mg, 0.72 mmol), and Cs_2CO_3 (176 mg, 0.54 mmol) under a nitrogen atmosphere. Freshly distilled dioxane was added (2.0 mL) followed by (*E*)-ethyl 3-chloro-2-iodobut-2-enoate **1**[5] (50 mg, 0.18 mmol), and the resulting mixture was heated at reflux for 4 h. The solution was cooled, diluted with Et_2O, and washed with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The pure product[22] (34 mg, 99%) was obtained as a clear oil by flash chromatography (hexanes then 1% Et_2O in hexanes): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.58−7.55 (m, 2H), 7.42−7.40 (m, 3H), 6.13 (q, J = 1.3 Hz, 1H), 4.17 (q, J = 7.0 Hz, 2H), 2.56 (d, J = 1.4 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H).

(*E*)-Ethyl 3-(4-Methoxyphenyl)but-2-enoate (5). Prepared from **1** (30 mg, 0.11 mmol), 4-methoxyphenylboronic acid (166 mg, 1.1 mmol), and Cs_2CO_3 (289 mg, 0.89 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (20 mg, 83%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.57−7.53 (m, 2H), 6.98−6.96 (m, 2H), 6.11 (q, J = 1.2 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 2.55 (d, J = 1.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.1 (C), 162.6 (C), 156.4 (C), 135.7 (C), 129.5 (CH), 116.7 (CH), 115.8 (CH), 61.0 (CH_2), 56.7 (CH_3), 18.5 (CH_3), 15.7 (CH_3); IR (neat) 1709, 1626 cm^{-1}; MS 220.1 (M$^+$); HRMS calcd for $C_{13}H_{16}O_3$ (M$^+$) 220.1099, found 220.1098.

(*E*)-Ethyl 3-(3-Methoxyphenyl)but-2-enoate (6). Prepared from **1** (30 mg, 0.11 mmol), 3-methoxyphenylboronic acid (166 mg, 1.1 mmol), and Cs_2CO_3 (289 mg, 0.89 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (19 mg, 79%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.33 (dd, J = 8.1, 0.3 Hz, 1H), 7.13 (ddd, J = 7.7, 1.7, 0.9 Hz, 1H), 7.09 (dd, J = 2.3, 0.3 Hz, 1H), 6.97 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.13 (q, 1.3 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 2.55 (d, J = 1.3 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.1 (C), 160.0 (C), 155.1 (C), 143.6 (C), 129.6 (CH), 118.5 (CH), 117.0 (CH), 114.7 (CH), 111.8 (CH), 59.4 (CH_2), 54.8 (CH_3), 17.1 (CH_3), 13.8 (CH_3); IR (neat) 1708, 1628 cm^{-1}; MS 220.1 (M$^+$); HRMS calcd for $C_{13}H_{16}O_3$ (M$^+$) 220.1099, found 220.1086.

(*E*)-Ethyl 3-(2-Methoxyphenyl)but-2-enoate (7). Prepared from **1** (30 mg, 0.11 mmol), 2-methoxyphenylboronic acid (166 mg, 1.1 mmol), and Cs_2CO_3 (289 mg, 0.89 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (24 mg, 98%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.35−7.31 (m, 1H), 6.97 (dd, J = 7.6, 1.6 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.97−6.93 (m, 1H), 5.82 (q, 1.2 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 2.45 (d, J = 1.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.8 (C), 158.3 (C), 158.1 (C), 134.6 (C), 131.5 (CH), 130.4 (CH), 122.4 (CH), 120.7 (CH), 113.2 (CH), 61.1 (CH_2), 56.8 (CH_3), 21.0 (CH_3), 15.6 (CH_3); IR (neat) 1712, 1630 cm^{-1}; MS 220.1 (M$^+$); HRMS calcd for $C_{13}H_{16}O_3$ (M$^+$) 220.1099, found 220.1091.

(*E*)-Ethyl 3-*p*-Tolylbut-2-enoate (8). Prepared from **1** (30 mg, 0.11 mmol), *p*-tolylboronic acid (149 mg, 1.1 mmol), and Cs_2CO_3 (289 mg, 0.89 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (17 mg, 76%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.48−7.45 (m, 2H), 7.24−7.22 (m, 2H), 6.12 (q, J = 1.2 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 2.55 (d, J = 1.2 Hz, 3H), 2.35 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.0 (C), 156.9 (C), 141.0 (C), 140.9 (C), 131.1 (CH), 128.0 (CH), 117.8 (CH), 61.1 (CH_2), 22.1 (CH_3), 18.7 (CH_3), 15.6 (CH_3); IR (neat) 1712, 1626 cm^{-1}; MS 204.1 (M$^+$); HRMS calcd for $C_{13}H_{16}O_2$ (M$^+$) 204.1150, found 204.1165.

(*E*)-Ethyl 3-(4-Fluorophenyl)but-2-enoate (9). Prepared from **1** (50 mg, 0.18 mmol), 4-fluorophenylboronic acid (255 mg, 1.8 mmol), and Cs_2CO_3 (445 mg, 1.4 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (26 mg, 69%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.66−7.63 (m, 2H), 7.21−7.16 (m, 2H), 6.12 (q, J = 1.2 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 2.56 (d, J = 1.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.9 (C), 165.1 (d, J = 245 Hz, C), 155.7 (C), 140.1 (d, J = 3.1 Hz, C), 130.3 (d, J = 8.4 Hz, CH), 118.7 (CH), 117.2 (d, J = 21.6 Hz, CH), 61.3 (CH_2), 18.8 (CH_3), 15.6 (CH_3); IR (neat) 1713, 1631 cm^{-1}; MS 208.1 (M$^+$); HRMS calcd for $C_{12}H_{13}FO_2$ (M$^+$) 208.0900, found 208.0905.

(2*E*,4*E*)-Ethyl 3-Methyl-5-phenylpenta-2,4-dienoate (10). Prepared from **1** (30 mg, 0.11 mmol), *trans*-styrenylboronic acid (161 mg, 1.1 mmol), and Cs_2CO_3 (289 mg, 0.9 mmol) using a procedure similar to that described for compound **3** that provided the known compound[23] as a colorless oil (21 mg, 88%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.61−7.59 (m, 2H), 7.40−7.36 (m, 2H), 7.33−7.29

(22) Paraskar, A. S.; Sudalai, A. *Tetrahedron* **2006**, *62*, 4907.

(23) Albaugh-Robertson, P.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 5288.

(m, 1H), 7.13−7.02 (m, 2H) 5.98 (s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.40 (d, J = 1.3 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H).

(*E*)-Ethyl 3-(Thiophen-2-yl)but-2-enoate (11). Prepared from **1** (50 mg, 0.18 mmol), thiophen-2-ylboronic acid (233 mg, 1.8 mmol), and Cs_2CO_3 (482 mg, 1.4 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (29 mg, 82%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.54 (dd, J = 5.1, 0.9 Hz, 1H), 7.48 (dd, J = 3.7, 1.0 Hz, 1H), 7.11 (dd, J = 5.1, 3.8 Hz, 1H), 6.22 (q, J = 1.1 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 2.58 (d, J = 1.2 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 165.9 (C), 145.6 (C), 145.0 (C), 128.3 (CH), 127.5 (CH), 127.3 (CH), 113.8 (CH), 59.4 (CH_2), 16.4 (CH_3), 13.8 (CH_3); IR (neat) 1716, 1607 cm^{-1}; MS 196.1 (M^+); HRMS calcd for $C_{10}H_{12}SO_2$ (M^+) 196.0558, found 196.0552.

(*E*)-Ethyl 3-(Naphthalene-2-ylbut-2-enoate (12). Prepared from **1** (30 mg, 0.11 mmol), naphthalen-1-ylboronic acid (188 mg, 1.1 mmol), and Cs_2CO_3 (289 mg, 0.89 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (25 mg, 96%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.95−7.87 (m, 3H), 7.56−7.47 (m, 3H), 7.34 (dd, J = 7.0, 1.1 Hz, 1H), 5.90 (q, J = 1.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.58 (d, J = 1.4 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 165.7 (C), 156.7 (C), 142.0 (C), 133.9 (C), 130.0 (C), 128.5 (CH), 128.2 (CH), 126.4 (CH), 126.1 (CH), 125.4 (CH), 125.1 (CH), 124.3 (CH), 120.4 (CH), 59.5 (CH_2), 20.9 (CH_3), 13.8 (CH_3); IR (neat) 1721, 1715 cm^{-1}; MS 240.1 (M^+); HRMS calcd for $C_{16}H_{16}O_2$ (M^+) 240.1150, found 240.1148.

(*E*)-Ethyl 3-(Naphthalene-2-yl)but-2-enoate (13). Prepared from **1** (30 mg, 0.11 mmol), naphthalen-2-ylboronic acid (188 mg, 1.1 mmol), and Cs_2CO_3 (289 mg, 0.89 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (14 mg, 54%): ^{1}H NMR (400 MHz, acetone-d_6) δ 8.13 (d, J = 1.6 Hz, 1H), 8.00−7.91 (m, 3H), 7.72 (dd, J = 8.7, 2.0 Hz, 1H), 7.57−7.53 (m, 2H), 6.31 (dd, J = 2.6, 1.3 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.68 (d, J = 1.3 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.1 (C), 154.8 (C), 139.2 (C), 133.7 (C), 133.4 (C), 128.6 (CH), 128.2 (CH), 127.5 (CH), 126.6 (CH), 126.5 (CH), 126.0 (CH), 123.9 (CH), 117.3 (CH), 59.4 (CH_2), 16.9 (CH_3), 13.8 (CH_3); IR (neat) 1721, 1640 cm^{-1}; MS 240.1 (M^+); HRMS calcd for $C_{16}H_{16}O_2$ (M^+) 240.1150, found 240.1147.

(*E*)-Ethyl 3-Cyclohexyl-3-phenylacrylate (15). Prepared from **14**[5] (28 mg, 0.08 mmol), phenylboronic acid (99 mg, 0.82 mmol), and Cs_2CO_3 (216 mg, 0.61 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (15 mg, 71%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.39−7.33 (m, 3H), 7.23−7.21 (m, 2H), 5.61 (q, J = 1.2 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.78 (ddt, J = 23.7, 11.8, 3.2 Hz, 1H), 1.76−1.62 (m, 5H), 1.42−1.23 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 1.13−1.06 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.2 (C), 167.3 (C), 143.2 (C), 129.7 (CH), 129.4 (CH), 129.3 (CH), 120.3 (CH), 61.3 (CH_2), 42.3 (CH), 33.3 (CH_2), 28.2 (CH_2), 27.6 (CH_2), 15.6 (CH_3); IR (neat) 1715, 1628 cm^{-1}; MS 258.2 (M^+); HRMS calcd for $C_{17}H_{22}O_2$ (M^+) 258.1620, found 258.1626.

(*E*)-Ethyl 5-(*tert*-butyldimethylsiloxy)-3-phenylpent-2-enoate (17). Prepared from **16**[5] (20 mg, 0.05 mmol), phenylboronic acid (58 mg, 0.48 mmol), and Cs_2CO_3 (126 mg, 0.36 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (13 mg, 81%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.58−7.55 (m, 2H), 7.44−7.39 (m, 3H), 6.11 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.74 (dd, J = 6.8, 6.8 Hz 2H), 3.70 (dd, J = 6.8, 6.8 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H), 0.82 (s, 9H), −0.02 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.6 (C), 159.0 (C), 143.2 (C), 130.8 (CH), 130.4 (CH), 128.7 (CH), 120.3 (CH), 63.9 (CH_2), 61.3 (CH_2), 36.1 (CH_2), 27.2 (CH_3), 19.7 (CH), 15.6 (CH_3), −4.3 (CH_3); IR (neat) 1716, 1618 cm^{-1}; MS 277.1 ($M^+ - C_4H_9$); HRMS calcd for $C_{15}H_{21}O_3Si$ ($M^+ - C_4H_9$) 277.1260, found 277.1269.

(*E*)-Ethyl 5-(Benzyloxy)-3-chloro-2-iodopent-2-enoate (18). A solution of ethyl 5-(benzyloxy)pent-2-ynoate[24] (500 mg, 2.16 mmol, 1.0 equiv) and tetrabutylammonium iodide (2.25 g, 6.09 mmol, 3.0 equiv) in dichloroethane (20 mL) was heated at reflux for 18 h. The reaction mixture was cooled, diluted with Et_2O, and washed with $NaHSO_3$ (20% solution), saturated $NaHCO_3$, and brine. The organic phase was then dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The pure product was obtained as a colorless oil (614 mg, 72%) by flash chromatography (hexanes and then 5% ether in hexanes): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.39−7.25 (m, 5H), 4.57 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 3.76 (dd, J = 6.3, 6.3 Hz, 2H), 3.02 (dd, J = 6.3, 6.3 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.8 (C), 140.5 (C), 136.2 (C), 130.1 (CH), 129.3 (CH), 129.2 (CH), 84.7 (C), 74.3 (CH_2), 63.8 (CH_2), 43.0 (CH_2), 15.2 (CH_3); IR (neat) 1728, 1618 cm^{-1}; MS 360.0 (M^+ − Cl); HRMS calcd for $C_{14}H_{16}ClIO_3$ (M^+ − Cl) 360.0222, found 360.0224.

(*E*)-Ethyl 5-(Benzyloxy)-3-phenylpent-2-enoate (19). Prepared from **18** (50 mg, 0.12 mmol), phenylboronic acid (149 mg, 1.2 mmol), and Cs_2CO_3 (324 mg, 0.92 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (38 mg, 96%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.58−7.56 (m, 2H), 7.42−7.40 (m, 3H), 7.31−7.23 (m, 5H), 6.11 (s, 1H), 4.46 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.59 (ddd, J = 12.8, 6.7, 0.7 Hz, 2H), 3.49−3.47(m, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.6 (C), 159.0 (C), 143.1 (C), 140.8 (C), 130.8 (CH), 130.4 (CH), 130.0 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 120.4 (CH), 73.9 (CH_2), 70.8 (CH_2), 61.4 (CH_2), 33.0 (CH_2), 15.6 (CH_3); IR (neat) 1705, 1622 cm^{-1}; this compound did not give satisfactory mass spectral data.

(*E*)-Ethyl 3-Chloro-2-iodo-5-(triisopropylsilyloxy)pent-2-enoate (20). Prepared from (*E*)-ethyl 5-(triisopropylsiloxy)pent-2-ynoate[25] (500 mg, 1.7 mmol) and tetrabutylammonium iodide (1.9 g, 5.0 mmol) using a procedure similar to that described for compound **18** that provided the title compound as a colorless oil (237 mg, 31%): ^{1}H NMR (400 MHz, acetone-d_6) δ 4.25 (q, J = 7.1 Hz, 2H), 4.03 (t, J = 6.2 Hz, 2H), 2.97 (t, J = 6.2 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.13−1.08 (m, 21H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.8 (C), 63.7 (CH_2), 62.0 (CH_2), 45.8 (CH_2), 19.4 (CH_3), 15.2 (CH_2), 13.7 (CH_3); IR (neat) 1732, 1620 cm^{-1}; MS 418.0 ($MH^+ - C_3H_7$); HRMS calcd for $C_{13}H_{24}ClIO_3Si$ ($MH^+ - C_3H_7$) 418.0228, found 417.9758.

(*E*)-Ethyl 3-Phenyl-5-(triisopropylsiloxy)pent-2-enoate (21). Prepared from **20** (50 mg, 0.11 mmol), phenylboronic acid (132 mg, 1.1 mmol), and Cs_2CO_3 (287 mg, 0.81 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (39 mg, 95%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.59−7.57 (m, 2H), 7.44−7.38 (m, 3H), 6.11 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.85 (dd, J = 6.8, 6.8 Hz, 2H), 3.42 (dd, J = 6.8, 6.8 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.03−0.99 (m, 21H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.6 (C), 159.1 (C), 143.3 (C), 130.8 (CH), 130.4 (CH), 128.8 (CH), 120.4 (CH), 64.4 (CH_2), 61.3 (CH_2), 36.2 (CH_2), 19.3 (CH_3), 15.6 (CH), 13.7 (CH_3); IR (neat) 1716, 1629 cm^{-1}; MS 333.2 ($M^+ - C_3H_7$); HRMS calcd for $C_{19}H_{29}O_3Si$ ($M^+ - C_3H_7$), 333.1886, found 333.1894.

(*E*)-3-Chloro-2-iodo-*N*-methoxy-*N*-methylnon-2-enamide (22). To a solution of 1-hexyne (2.6 mL, 17.7 mmol) in hexanes (150 mL) at −78 °C was added a solution of butyllithium (2.26 M in THF, 8.63 mL, 19.5 mmol). After 1 h, a solution of *N*-methoxy-*N*-methylcarbamoyl chloride[26] (2.40 g, 19.4 mmol) in THF (20 mL) was slowly added via canula. The reaction was stirred for 1 h at −78 °C, and then the reaction was quenched by the dropwise addition of 10% HCl. The mixture was allowed to warm to room

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temperature for 1 h and was then diluted with ether. The organic layer was washed sequentially with a saturated solution of sodium bicarbonate and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The pure amide was obtained by chromatography eluting with 5% EtOAc in hexanes then 20% EtOAc in hexanes to give a pale yellow oil (3.02 g, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 2.94 (s, 3H), 2.03 (t, J = 6.4 Hz, 2H), 1.36 - 1.14 (m, 8H), 0.93 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.0 (CH_3), 61.8 (CH_3), 31.1 (CH_2), 30.8 (CH_2), 28.4 (CH_2), 27.6 (CH_2), 22.4 (CH_2), 18.8 (CH_2), 13.6 (CH_3); IR (neat) 2237, 1644 cm^{-1}; MS 197.1 (M^+); HRMS calcd for $C_{11}H_{19}NO_2$ (M^+) 197.1416, found 197.1405. This material was transformed into the title compound using a procedure similar to that described above for compound **18** that provided the desired material as a colorless oil (5.05 g, 92%): ^{1}H NMR (400 MHz, C_6D_6) δ 3.22 (s, 3H), 2.82 (s, 3H), 2.46 (br, 2H), 1.48 - 1.45 (m, 2H), 1.19 - 1.14 (m, 6H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 166.3 (C), 135.1 (C), 82.7 (C), 60.8 (CH_3), 40.4 (CH_2), 32.4 (CH_3), 31.8 (CH_2), 28.3 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 14.1 (CH_3); IR (neat) 2954, 2930 cm^{-1}; MS 359.0 (M^+); HRMS calcd for $C_{11}H_{19}ClINO_2$ (M^+) 359.0149, found 359.0201.

(*E*)-*N*-Methoxy-*N*-methyl-3-phenylnon-2-enamide (23). Prepared from **22** (50 mg, 0.11 mmol), phenylboronic acid (132 mg, 1.1 mmol), and Cs_2CO_3 (287 mg, 0.81 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (39 mg, 99%): ^{1}H NMR (400 MHz, C_6D_6) δ 7.35 (dd, J = 6.6, 1.6 Hz, 2H), 7.15−7.08 (m, 3H), 6.65 (s, 1H), 3.34 (t, J = 7.7 Hz, 2H), 3.06 (s, 3H), 2.97 (s, 3H), 1.65−1.57 (m, 2H), 1.45−1.38 (m, 2H), 1.24−1.19 (m, 4H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 167.1 (C), 158.0 (C), 143.1 (C), 128.7 (CH), 128.3 (CH), 127.1 (CH), 117.0 (CH), 60.9 (CH_3), 54.8 (CH_3), 31.9 (CH_2), 31.4 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 23.0 (CH_2), 14.2 (CH_3); IR 1731, 1649 cm^{-1}; MS 275.1 (M^+); HRMS calcd for $C_{17}H_{25}NO_2$ (M^+) 275.1885, found 275.1891.

(*E*)-*N*-Methoxy-3-(4-methoxyphenyl)-*N*-methylnon-2-enamide (24). Prepared from **22** (50 mg, 0.11 mmol), 4-methoxyphenylboronic acid (132 mg, 1.1 mmol), and Cs_2CO_3 (287 mg, 0.81 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (39 mg, 92%): ^{1}H NMR (400 MHz, C_6D_6) δ 7.37 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 6.71 (s, 1H), 3.39 (t, J = 7.6 Hz, 2H), 3.27 (s, 3H), 3.10 (s, 3H), 3.00 (s, 3H), 1.73−1.69 (m, 2H), 1.49−1.44 (m, 2H), 1.27−1.24 (m, 4H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 168.0 (C), 160.6 (C), 157.6 (C), 135.1 (C), 128.3 (CH), 115.3 (CH), 114.2 (CH), 60.9 (CH_3), 54.8 (CH_3), 32.0 (CH_2), 31.3 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 23.0 (CH_2), 14.3 (CH_3); IR 1731, 1649 cm^{-1}; MS 305.2 (M^+); HRMS calcd for $C_{18}H_{27}NO_3$ (M^+) 305.1991, found 305.1988.

(*E*)-Ethyl 2-Iodo-3-phenylbut-2-enoate (29). To an oven-dried, 25 mL, round-bottom flask equipped with a magnetic stirring bar were added CuI (96 mg, 0.503 mmol), freshly distilled tetrahydrofuran (4.0 mL), and methyllithium (1.6 M in Et_2O, 0.63 mL, 1.00 mmol), and the resulting mixture was cooled to −78 °C. To this mixture was added, via cannula, a solution of ethyl 3-phenylpropiolate (88 mg, 0.5 mmol) in tetrahydrofuran (1.0 mL). The resulting mixture was stirred at −78 °C for 1 h, and then iodine (381 mg, 1.50 mmol) was introduced. The solution was stirred briefly at −78 °C and was then allowed to warm to 0 °C and was stirred at that temperature for 2 h. The reaction mixture was then diluted with Et_2O and washed with saturated aqueous NH_4Cl. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The pure product was obtained as a clear oil (152 mg, 96%) by flash chromatography (5% Et_2O in hexanes): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.36−7.33 (m, 3H), 7.25−7.22 (m, 2H), 3.88 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.1 (C), 152.2 (C), 142.7 (C), 130.1 (CH), 129.9 (CH), 128.8 (CH), 63.1 (CH_2), 16.6 (CH_3), 14.7 (CH_3); IR (neat) 1720, 1629 cm^{-1}; MS 316.0 (M^+); HRMS calcd for $C_{12}H_{13}IO_2$ (M^+) 315.9960, found 315.9980.

(*Z*)-Ethyl 2-(4-Methoxyphenyl)-3-phenylbut-2-enoate (30). Prepared from **29** (70 mg, 0.22 mmol), phenylboronic acid (270 mg, 2.2 mmol), and Cs_2CO_3 (586 mg, 1.7 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (50 mg, 85%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.38−7.18 (m, 7H), 6.97 (d, J = 8.8 Hz, 2H), 3.82 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.05 (s, 3H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 170.9 (C), 161.1 (C), 145.1 (C), 143.0 (C), 134.7 (C), 132.2 (CH), 131.3 (C), 129.9 (CH), 129.1 (CH), 129.0 (CH), 115.5 (CH), 61.7 (CH_2), 56.5 (CH_3), 23.1 (CH_3), 14.9 (CH_3); IR (neat) 1709, 1602 cm^{-1}; MS 296.1 (M^+); HRMS calcd for $C_{19}H_{20}O_3$ (M^+) 296.1412, found 296.1405.

(*E*)-Ethyl 3-Phenyl-2-deuterobut-2-enoate (34). Prepared from **1** (50 mg, 0.18 mmol) and $C_6H_5B(OD)_2$[27] (89 mg, 0.72 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (21 mg, 60%): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.58−7.56 (m, 2H), 7.45−7.39 (m, 3H), 6.13 (q, J = 1.3 Hz, 0.48H), 4.17 (q, J = 7.2 Hz, 2H), 2.57 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 167.9 (C), 156.9 (C), 143.8 (C), 130.9 (CH), 130.4 (CH), 128.1 (CH), 118.7 (CH), 61.2 (CH_2), 18.8 (CH_3), 15.6 (CH_3); IR (neat) 1711, 1617 cm^{-1}; MS 191.1 (M^+); HRMS calcd for $C_{12}H_{13}DO_2$ (M^+) 191.1057, found 191.1043.

(*E*)-Ethyl 3-(Pentadeuterophenyl)but-2-enoate (35). Prepared from **1** (50 mg, 0.18 mmol) and $C_6D_5B(OH)_2$ (89 mg, 0.72 mmol) using a procedure similar to that described for compound **3** that provided the title compound as a colorless oil (33 mg, 98%): ^{1}H NMR (400 MHz, acetone-d_6) δ 6.14 (dd, J = 1.4 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 2.56 (dd, J = 1.4 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 167.9 (C), 156.9 (C), 143.8 (C), 129.9 (CD, J = 14.7 Hz), 127.7 (CD, J = 14.7 Hz), 118.6 (CH), 61.2 (CH_2), 18.8 (CH_3), 15.6 (CH_3); IR (neat) 1712, 1626 cm^{-1}; MS 195.1 (M^+); HRMS calcd for $C_{12}H_9D_5O_2$ (M^+) 195.1308, found 195.1308.

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Supporting Information Available: Experimental procedures and product characterization data for *E* isomers. ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) $C_6H_5B(OD)_2$ was prepared by recrystallizing $C_6H_5B(OH)_2$ from boiling D_2O. The boronic acid so obtained was dried under vacuum over P_2O_5 for 16 h before use. NMR indicated 52% deuterium incorporation.